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(54) Indazole-3-carboxamide and -3-carboxylic acid derivatives

Derivate von Indazole-3-carboxamide und -3-carboxylsäure

Dérivés d'indazole-3-carboxamide et de l'amide-3-carboxylique

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(56) References cited:
EP-A- 0 214 772
EP-A- 0 223 385
WO-A-84/00166
WO-A-85/01048

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Description

[0001] The present invention relates to novel, structurally distinct compounds having 5-HT antagonist activity, to processes for their preparation and their use as pharmaceuticals.

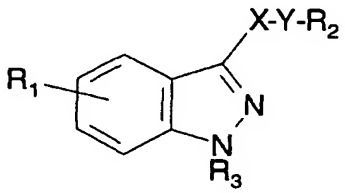
[0002] Compounds usefull in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis are already disclosed in the prior art. More specifically, compounds exhibiting 5-HT antagonist properties are known.

[0003] The International Patent Application WO 85/01048 relates to compounds having an 5-HT antagonist activity in which an azabicyclic moiety is attached to an aryl or heteroaryl moiety through an ester or amide link.

[0004] The International Patent Application WO 84/00166 describes compounds having an 5-HT antagonist activity in which an azabicyclic moiety is attached to an indole moiety through an ester or amide link.

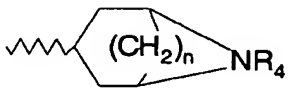
[0005] A class of novel, structurally distinct compounds has been discovered. Surprisingly, these compounds comprising both an azabicyclic moiety and an heteroaryl moiety present 5-HT antagonist activity and/or gastric moiety enhancing activity.

[0006] Accordingly, the present invention provides compound of formula (I), or a pharmaceutically acceptable salt thereof:

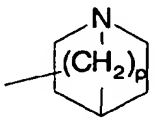


wherein

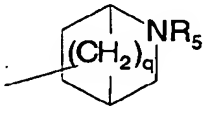
X is CO and Y is NH or O;
R_3 is hydrogen, C_{1-6} alkyl, C_{3-7} alkenyl-methyl, phenyl or phenyl C_{1-4} alkyl either of which phenyl moieties may be substituted by one or two of halogen, CF_3, C_{1-6} alkoxy or C_{1-6} alkyl;
R_1 is hydrogen, halogen, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy;
R_2 is a group of formula (a), (b) or (c):



(a)



(b)



(c)

wherein n is 2 or 3;

p and q are independently 1 to 3;
and
R_4 or R_5 is C_{1-3} alkyl.

[0007] Values for R_1 include hydrogen, chloro, bromo, CF_3, methyl, ethyl, methoxy, ethoxy.

[0008] Values for R_3 include hydrogen, methyl, ethyl, prop-1-enyl-methyl, prop-2-enyl-methyl, but-1-enyl-methyl, but-3-enyl-methyl, benzyl, phenyl, 4-chloro-phenyl-methyl, 3,5-dichloro-phenyl-methyl, CF_3, methyl, ethyl, methoxy, ethoxy, for example.

[0009] Preferably, R_3 is hydrogen or methyl.

[0010] Preferably, R_2 is a group of formula (a) wherein R_4 is as above defined.

[0011] It will be realised that in the compound of the formula (I) the -X-Y-linkage may have an endo or exo orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventonally therefrom e.g. by chromatography; or alternatively the endo and exo isomer may if desired by synthesised from the corresponding isomer of the compound of the formula (VI).

[0012] Preferably, Y-R_2 is in the *endo*-configuration.

[0013] In another preferred embodiment, when R_2 is a group of formula (c) and q is 1 or 2.

[0014] In another preferred embodiment, when R_2 is of formula (a) or (c) and R_4 or R_5 is replaced by hydrogen.

[0015] The pharmaceutically acceptable salts of the compound of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

[0016] The pharmaceutically acceptable salts of the compound of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulfuric, citric, tartaric, lactic and acetic acid.

[0017] Preferably the acid addition salt is the hydrochloride salt.

[0018] Examples of pharmaceutically acceptable salts include quaternary derivatives of the compound of formula (I) such as the compounds quaternised by compounds R_{10}-T wherein R_{10} is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_{10} include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

[0019] Examples of pharmaceutically acceptable salts of the compound of formula (I) also form internal salts such as pharmaceutically acceptable N-oxides.

[0020] The compound of the formula (I) and its pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included whenever the compound and salts are herein referred to.

[0021] Examples of the variables and preferred variables are listed below;

3-Indazolecarboxylic acid (*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ester,

N-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)indazole-3-carboxamide,

1-methyl-3-indazolecarboxylic acid(*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ester,

N-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5-fluoroindazole-3-carboxamide,

N-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5-chloroindazole-3-carboxamide,

N-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-ethylindazole-3-carboxamide,

5α-N-(2-methyl-2-azabicyclo[2.2.2]oct-5-yl)-1-methylindazole-3-carboxamide,

N-(*exo*-2-methyl-2-azabicyclo[2.2.1]hept-5-yl)-1-methylindazole-3-carboxamide,

N-(*endo*-2-methyl-2-azabicyclo[2.2.1]hept-5-yl)-1-methylindazole-3-carboxamide,or

a pharmaceutically acceptable salt of any of the foregoing.

[0022] The compound of the present Invention is a 5-HT antagonist and it is thus believed may generally be used in the treatment or prophylaxis of migraine, cluster headaches and trigeminal neuralgia; and also as an anti-emetic, in particular that of preventing vomiting and nausea associated with cancer therapy. Examples of such cancer therapy

include that using cytotoxic agents, such as cisplatin, doxorubicin and cyclophosphamide, particularly cisplatin; and also radiation treatment. Compounds which are 5-HT antagonists may also be of potential use in the treatment of CNS disorders such as anxiety and psychosis; arrhythmia, obesity and irritable bowel syndrome.

[0023] The compounds of the present invention also have gastric motility enhancing activity, useful in the treatment of disorders such as retarded gastric emptying, dyspepsia, flatulence, oesophagal reflux and peptic ulcer.

[0024] The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0025] Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

[0026] Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colorants, flavorings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

[0027] Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

[0028] Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulfate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or coloring agents.

[0029] Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavoring or coloring agents.

[0030] The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

[0031] For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilizing before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

[0032] Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilized by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

[0033] The invention further provides use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as a 5-HT antagonist.

[0034] In particular, such medicaments are use for treatment or prophylaxis of migraine, cluster headache, trigeminal neuralgia and/or emesis in mammals.

[0035] An amount effective to treat the disorders hereinbefore described depends on the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.5 to 1000mg for example 1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.001 to 50 mg/kg/day, more usually 0.002 to 25 mg/kg/day.

[0036] No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

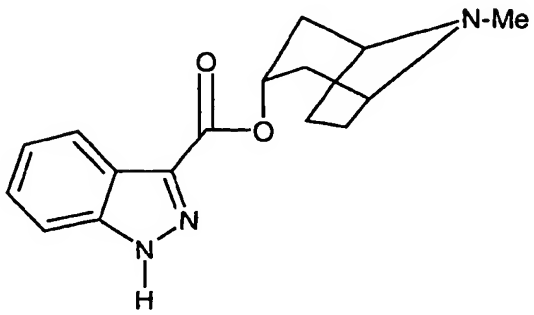
[0037] The following Examples illustrate the preparation of the compound of formula (I).

[0038] N.B. Nomenclature is based on Chemical Abstracts Index Guide 1977 published by the American Chemical Society.

Example 1

3-Indazolecarboxylic acid (endo-8-methyl-8-azabiclo[3.2.1]oct-3-yl)ester (E1)

[0039]



(E1)

[0040] A solution of tropine (0.45 g) and KBu^{t}O (0.36 g) in amine-free DMF (50 ml) was stirred at room temperature for 30 min. The more volatile t-butanol was removed by rotary evaporation and the residual solution treated with diindazolo[2,3-a 2',3'-d]-pyrazine-7,14-dione (0.2 g). After heating to 120° for 2 h, the reaction mixture was cooled, evaporated to dryness and the residue treated with saturated $NaHCO_3$ solution (50 ml). The pH was adjusted to ca.8 with acetic acid and the product extracted into $CHCl_3$ (3×100 ml). The organic extracts were dried (Na_2SO_4), evaporated to dryness and the residue triturated with diethylether to give E1 (0.16 g) mp 234°-235° (dec).

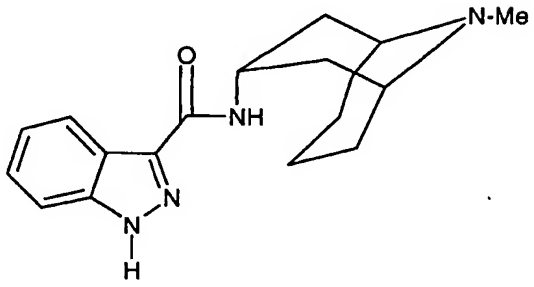
^{1}H NMR (270 MHz, d_6 -DMSO)

δ	13.5 (1H, brs)
	8.18 (1H, d)
	7.60 (1H, d)
	7.39 (1H, t)
	7.28 (1H, t)
	5.31 (1H, t)
	3.23 (2H, brs)
	2.36 (3H, s)
	2.45-1.90 (8H, m)

Example 2

N-(Endo-9-methyl-9-azabicyclo[3,3,1]non-3-yl)indazole-3-carboxamide (E2)

[0041]



(E2)

[0042] A suspension of diindazolo[2,3-a,2',3'-d)pyrazin-7,14-dione (0.76 g) in DMF (20 ml) was heated with endo-9-methyl-9-azabicyclo[3,3,1]nonan-3-amine (0.31 g) for 2 h at 100°C. After evaporation to dryness, the residue was purified by column chromatography (TLC grade alumina, $CHCl_3$) to give the title compound (E2) (0.12 g) m.p. 209°-212° C.

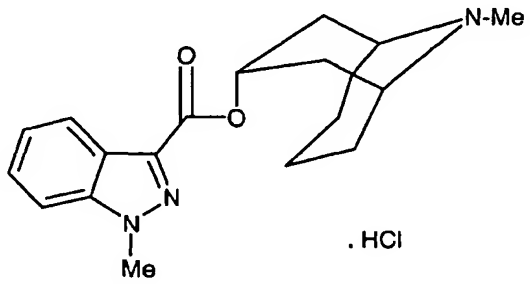
^1H NMR (270 MHz, $CDCl_3$).

δ 13.01 (brs, 1H)
8.30 (d, 1H)
7.54 (d, 1H)
7.35 (t, 1H)
7.20 (t, 1H)
7.10 (d, 1H)
4.54 (dtt, 1H)
3.12 (brd, 2H)
2.60-2.40 (m, 5H including 2.53, s, 3H)
2.10-1.90 (m, 3H)
1.60-1.35 (m, 3H)
1 15-1.00 (m, 2H)

Example 3

1-Methyl-3-indazolecarboxylic acid (endo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl)ester monohydrochloride (E3)

[0043]



(E3)

[0044] Following the procedure outlined in Example 1, the potassium salt of tropine (0.37 g) was reacted with 1-methyl-3-indazolcarboxylic acid chloride (0.21 g) to give, after treatment with ethanolic hydrogen chloride, the title compound (E3) (0.21 g) m.p. 257°-260° C.

^{1}H NMR (79.5 MHz, $CDCl_3$)

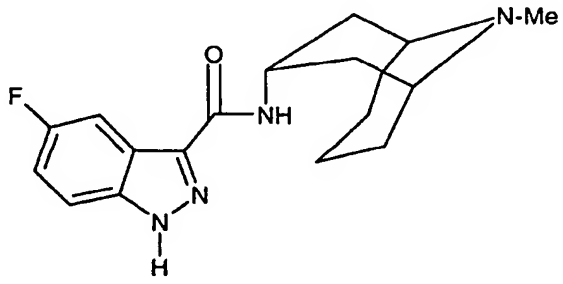
δ 8.30-8.10 (m, 1H)
7.60-7.20 (m, 3H)
5.55-5.30 (m, 1H)
4.18 (s, 3H)
4.00-3.70 (m, 2H)
3.40-2.00 (m, 11H including 2.83, s, 3H).

[0045] Following the procedure outlined in Example 2, the following compounds were prepared:

Example 4

N-(Endo-9-methyl-9-azabicyclo[3,3,1]non-3-yl)-5-fluoroindazole-3-carboxamide (E4)

[0046]



(E4)

m.p. 264°-267° C. (dec.)

^{1}H NMR (79.5 MHz, $CDCl_3$ +(CD3)2 SO)

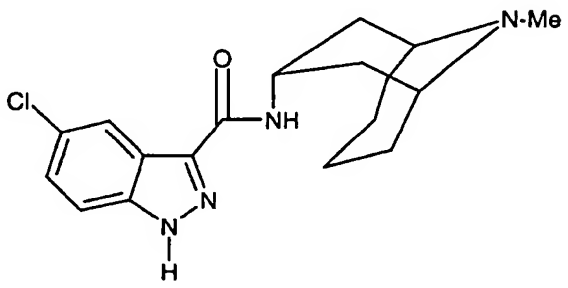
δ 13.30 (brs, 1H)

7.92 (dd. 1H)
7.53 (m, 1H)
7.30-6.95 (m, 2H)
4.80-4.20 (m, 1H)
3.30-2.90 (m, 2H)
2.70-0.80 (m, 13H including 2.52, s, 3H).

Example 5

N-(Endo-9-methyl-9-azabicyclo[3,3,1]non-3-yl)-5-chloroindazole-3-carboxamide (E5)

[0047]



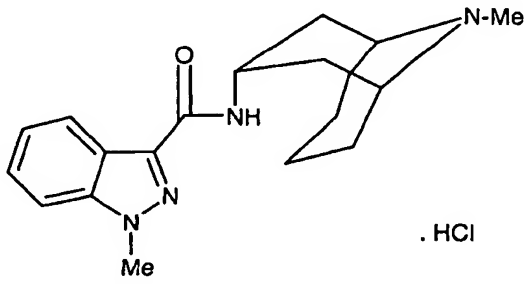
(E5)

^{1}H NMR (79.5 MHz, $CDCl_3$ +$(CD_3)_2$ SO)
δ 13.50 (brs, 1H)
8.25 (brs, 1H)
7.80-7.25 (m, 3H)
4.75-4.20 (m, 1H)
3.50-2.80 (m, 2H)
2.65-0.80 (m, 13H including 2.49, s, 3H).

Example 6

N-(Endo-9-methyl-9-azabicyclo[3,3,1]non-3-yl)-1-methylindazole-3-carboxamide monohydrochloride (E6)

[0048]



(E6)

[0049] A stirred solution of 1-methylindazole-3-carboxylic acid chloride (0.77 g) in dichloromethane (50 ml) was treat-

ed with a solution of endo-9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (0.7 g) and triethylamine (0.7 ml) in dichloromethane (30 ml). After 2 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (100 ml) and dried (K_2CO_3). The oil remaining after evaporation of the solvent was purified by column chromatography (TLC-alumina, $CHCl_3$) and treated with hydrogen chloride to give the title compound E6. m.p. 290°-292°C.

^1H NMR (270 MHz, $CDCl_3$)

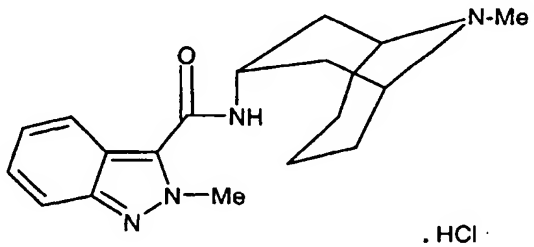
δ 8.30 (d, 1H)
7.50-7.20 (m, 4H)
4.80-4.50 (m, 1H)
4.12 and 4.10 (2-s, 3H)
3.75-3.55 (m, 2H)
2.99 and 2.91 m (2-s, 3H)
2.82-2.40 (m, 4H)
2.20-2.00 (m, 2H)
1.90-1.60 (m, 4H)

[0050] Following the procedure outlined in Example 6, the following compounds were prepared:

Example 7

N-(Endo-9-methyl-9-azabicyclo[3,3,1]non-3-yl)-2-methylindazole-3-carboxamide monohydrochloride (E7)

[0051]



. HCl

(E7)

m.p. 271-2°C

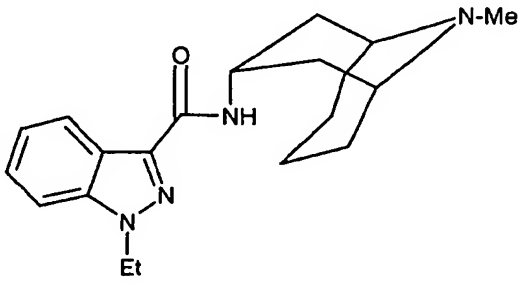
^1H NMR (270 MHz, $(CD_3)_2SO$)

δ 11.25-10.30 (2s, 1H)
8.72, 8.45 (2d, 1H)
8.80 (d, 1H)
8.68 (d, 1H)
7.36-7.15 (m, 2H)
5.05-4.90 (m, 1H)
4.70-4.55
4.39 (s, 3H)
3.67 (brd, 2H)
2.99-2.90 (2d, 3H)
2.80-2.50 (m, 3H)
2.40-1.90 (m 4H)
1.80-1.50 (m, 3H)

Example 8

N-(Endo-9 -methyl -9-azabicyclo[3,3,1]non-3-yl)-1-ethylindazole-3 -carboxamide (E8)

[0052]



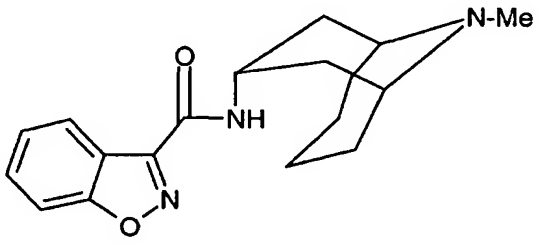
(E9)

^{1}H NMR (79.5 MHz, $CDCl_3$)
δ 8.42 (dm, 1H)
7.55-7.10 (m, 3H),
6.80 (brd, 1H)
4.80-4.20 (m, 3H including 4.42, q, 2H)
3.30-2.90 (m, 2H)
2.75-2.30 (m, 5H including 2.55, s, 3H)
2.20-0.90 (m, 11H including 1.54, t, 3H)

Example 9

N-(Endo-9-methyl-9-azabicyclo[3,3,1]non-3-yl)-1,2-benzisoxazole-3-carboxamide (E9)

[0053]



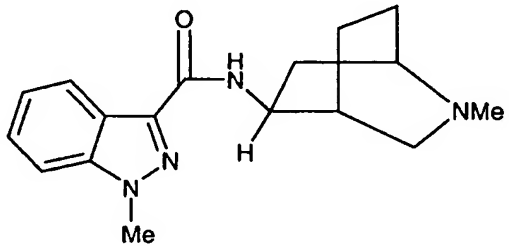
(E9)

m.p. 126-8°C
^{1}H NMR (79.5 MHz, $CDCl_3$)
δ 8.35 (dm, 1H)
7.80-7.25 (m, 3H)
6.80 (brd, 1H)
4.80-4.30 (m, 1H)
3.35-3.00 (m, 2H)
2.80-2.25 (m, 5H including 2.56, s, 3H)
2.20-0.90 (m, 8H)

Example 10

5α--N-(2-methyl-2-azabicyclo[2,2,2]oct-5-yl)-1-methyl-indazole-3-carboxamide(E10)

[0054]



(E10)

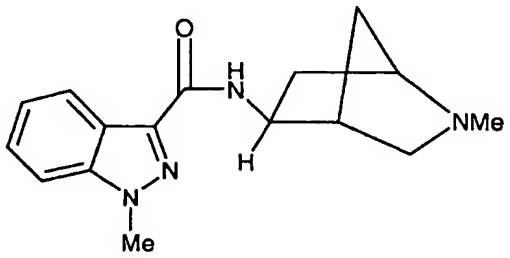
^{1}H NMR (270 MHz, $CDCl_3$)

δ	8.36 (dm, 1H)
	7.50-7.49 (m, 2H)
	7.33-7.24 (m, 1H)
	7.05 (brd, 1H)
	4.48-4.35 (m, 1H)
	4.10 (s, 3H)
	2.90 (brs, 2H)
	2.76-2.60 (m, 2H)
	2.45 (s, 3H)
	2.15-2.00 (m, 2H)
	1.95-1.80 (m, 1H)
	1.71-1.55 (m, 2H)
	1.44-1.34 (m, 1H)

Example 11

N-(Exo-2-methyl-2-azabicyclo[2,2,1]hept-5-yl)-1-methylindazole-3-carboxamide monohydrochloride (E11)

[0055]



(E11)

^{1}H NMR (270 MHz, $CDCl_3$)

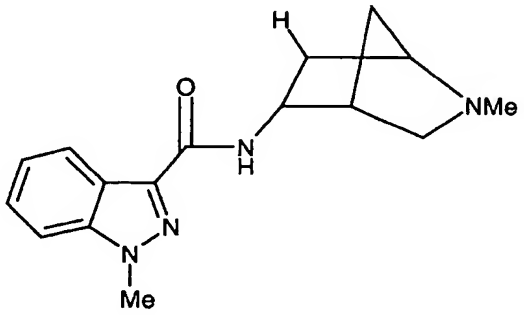
δ	13.00-12.50 (m, 1H)

8.28 (d, 1H)
7.50-7.20 (m, 3H)
6.82 (brs, 1H)
5.10-4.60 (m, 1H)
4.20-3.70 (m, 4H including 4.09, s, 3H)
3.30-1.70 (m, 10H).

Example 12

N-(Endo-2-methyl-2-azabicyclo[2,2,1]hept-5-yl)-1-methylindazole-3-carboxamide monohydrochloride (E12)

[0056]



(E12)

^{1}H NMR (270 MHz, $CDCl_3$)
δ 12.40-12.10 (m, 1H)
8.40-8.20 (m, 2H)
7.50-7.20 (m, 3H)
4.72-4.55 (m, 1H)
4.22 (d, 1H)
4.13 (s, 3H)
3.80 (s, 1H)
3.21 (s, 1H)
3.00-2.85 (m, 4H including 2.80, s, 3H)
2.61 (d, 1H)
2.26 (t, 1H)
2.16-1.80 (m, 2H)

Pharmacology

Antagonism of the von Bezold-Jarisch reflex

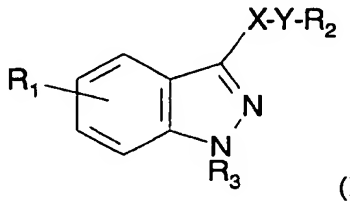
[0057] The compounds were evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

[0058] Male rats 250-350 g, were anaesthetised with urethane (1.25 g/kg intraperitoneally) and blood pressure and heart rate recorded as described by
Fozard J. R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6 μg/kg) was given repeatedly by the
intravenous route and changes in heart rate quantified. Compounds were given intravenously and the concentration required to reduce the 5 HT-evoked response to 50% of the control response (ED50) was then determined.
The results were as follows.

Compound No.	ED_{50} (mg/kg)
1	0.0005
2	0.0011
3	0.0014
5	0.015
6	0.0007
8	0.0006
10	0.0017
11	0.01

Claims

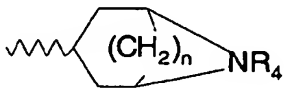
1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



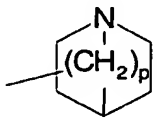
(I)

wherein

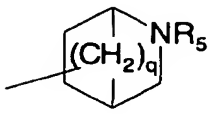
X is CO and Y is NH or O;
R_3 is hydrogen, C_{1-6} alkyl, C_{3-7} alkenyl-methyl, phenyl or phenyl C_{1-4} alkyl either of which phenyl moieties may be substituted by one or two of halogen, CF_3, C_{1-6} alkoxy or C_{1-6} alkyl;
R_1 is hydrogen, halogen, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy;
R_2 is a group of formula (a), (b) or (c):



(a)



(b)



(c)

wherein n is 2 or 3;
p and q are independently 1 to 3;
and
R_4 or R_5 is C_{1-3} alkyl.

2. A compound according to claim 1 wherein R_2 is a group of formula (a).

3. A compound according to claim 2 wherein Y-R_2 is in the *endo*-configuration.

4. A compound according to claim 1 wherein R_2 is a group of formula (c) wherein q is 1 or 2.

5. A compound according to any one of claims 1 to 4 wherein R_3 is hydrogen or methyl.

6. A compound according to any one of claims 1 to 5 wherein R_1 is hydrogen or 5-halo.

7. 3-Indazolecarboxylic acid (*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ester,

N-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)indazole-3-carboxamide,

1-methyl-3-indazolecarboxylic acid(*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ester,

N-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5-fluoroindazole-3-carboxamide,

N-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-5-chloroindazole-3-carboxamide,

N-(*endo*-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-ethylindazole-3-carboxamide,

5α-N-(2-methyl-2-azabicyclo[2.2.2]oct-5-yl)-1-methylindazole-3-carboxamide,

N-(*exo*-2-methyl-2-azabicyclo[2.2.1]hept-5-yl)-1-methylindazole-3-carboxamide,

N-(*endo*-2-methyl-2-azabicyclo[2.2.1]hept-5-yl)-1-methylindazole-3-carboxamide, or

a pharmaceutically acceptable salt of any of the foregoing.

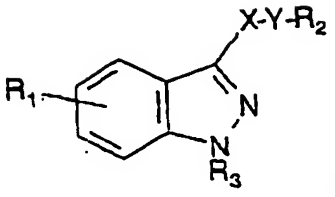
8. A compound of formula (I) wherein R_2 is of formula (a) or (c) as defined in claim 1, but wherein R_4 or R_5 is replaced by hydrogen.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. Use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for use as a 5-HT antagonist.

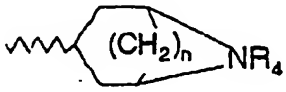
Patentansprüche

1. Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon:

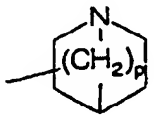


(I)

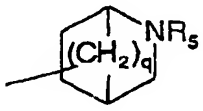
wobei X für CO und Y für NH oder für O steht;
R_3 ein Wasserstoffatom, ein C_{1-6}-Alkyl-, ein C_{3-7}-Alkenylmethylrest, eine Phenylgruppe oder ein Phenyl-C_{1-4}-alkylrest ist, wobei jede der Phenyleinheiten durch ein oder zwei Halogenatome, CF_3, einen C_{1-6}-Alkoxy- oder C_{1-6}-Alkylrest substituiert sein kann;
R_1 ein Wasserstoffatom, Halogenatom, CF_3, ein C_{1-6} -Alkyl- oder C_{1-6} -Alkoxyrest ist;
R_2 ein Rest der Formel (a), (b) oder (c) ist:



(a)



(b)



(c)

wobei n für 2 oder 3 steht;
p und q unabhängig voneinander 1 bis 3 bedeuten;
und R_4 oder R_5 einen C_{1-3}-Alkylrest bedeutet.

2. Verbindung gemäß Anspruch 1, wobei R_2 ein Rest der Formel (a) ist.

3. Verbindung gemäß Anspruch 2, wobei Y-R_2 in *endo*-Konfiguration vorliegt.

4. Verbindung gemäß Anspruch 1, wobei R_2 ein Rest der Formel (c) ist, in der q für 1 oder 2 steht.

5. Verbindung gemäß einem der Ansprüche 1 bis 4, wobei R_3 ein Wasserstoffatom oder eine Methylgruppe ist.

6. Verbindung gemäß einem der Ansprüche 1 bis 5, wobei R_1 ein Wasserstoffatom oder ein 5-Halogenatom ist.

7. 3-Indazolcarbonsäure (*endo*-8-Methyl-8-azabicyclo [3.2.1]oct-3-yl) ester;

N-(*endo*-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)indazol-3-carboxamid,

1-Methyl-3-indazolcarbonsäure(*endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)ester,
N-(*endo*-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-5-fluorindazol-3-carboxamid,
N-(*endo*-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-5-chlorindazol-3-carboxamid,
N-(*endo*-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-1-ethylindazol-3-carboxamid,
5α-N-(2-Methyl-2-azabicyclo[2.2.2]oct-5-yl)-1-methylindazol-3-carboxamid,
N-(*exo*-2-Methyl-2-azabicyclo[2.2.1]hept-5-yl)-1-methylindazol-3-carboxamid,
N-(*endo*-2-Methyl-2-azabicyclo[2.2.1]hept-5-yl)-1-methylindazol-3-carboxamid,

oder ein pharmazeutisch verträgliches Salz einer der vorstehenden Verbindungen.

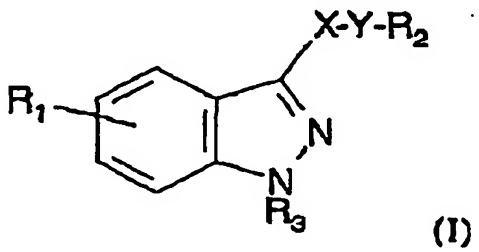
8. Verbindung der Formel (I) gemäß Anspruch 1, wobei R_2 die Formel (a) oder (c), aufweist, wobei jedoch R_4 oder R_5 durch ein Wasserstoffatom ersetzt ist.

9. Arzneimittel, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 7 oder ein pharmazeutisch verträgliches Salz davon und einen pharmazeutisch verträglichen Träger.

10. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 7 bei der Herstellung eines Medikaments zur Verwendung als 5-HT Antagonist.

Revendications

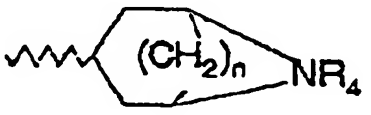
1. Composé de formule (I), ou sel acceptable d'un point de vue pharmaceutique de ce dernier :



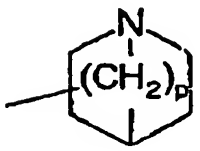
(I)

dans laquelle

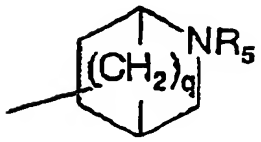
X est CO, et Y est NH ou O ;
R_3 est un atome d'hydrogène ou un groupe alkyle en C_{1-6}, (alcényle en C_{3-7})méthyle, phényle, ou phényl (alkyle en C_{1-4}), le fragment phényle de l'un ou de l'autre pouvant être substitué par un ou deux substituants halogène, CF_3, alcoxy en C_{1-6} ou alkyle en C_{1-6} ;
R_1 est un atome d'hydrogène ou d'halogène, CF_3 ou un groupe alkyle en C_{1-6} ou alcoxy en C_{1-6} ;
R_2 est un groupe ayant la formule (a), (b) ou (c) :



(a)



(b)



(c)

où n vaut 2 ou 3 ;
p et q valent chacun indépendamment de l'autre 1 à 3 ; et
R_4 ou R_5 est un groupe alkyle en C_{1-3}.

2. Composé selon la revendication 1, dans lequel R_2 est un groupe de formule (a).

3. Composé selon la revendication 2, dans lequel Y-R_2 est en configuration endo.

4. Composé selon la revendication 1, dans lequel R_2 est un groupe de formule (c) dans laquelle q vaut 1 ou 2.

5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel R_3 est un atome d'hydrogène ou le groupe méthyle.

6. Composé selon l'une quelconque des revendications 1 à 5, dans lequel R_1 est un atome d'hydrogène ou un substituant 5-halogéno.

7. Ester (endo-8-méthyl-8-azabicyclo[3.2.1]oct-3-yl) de l'acide 3-indazole carboxylique,

N-(endo-9-méthyl-9-azabicyclo[3.3.1]non-3-yl) indazole-3-carboxamide,
ester (endo-8-méthyl-8-azabicyclo[3.2.1]oct-3-yl) de l'acide 1-méthyl-3-indazole carboxylique,
N-(endo-9-méthyl-9-azabicyclo[3.3.1]non-3-yl)-5-fluoroindazole-3-carboxamide,
N-(endo-9-méthyl-9-azabicyclo[3.3.1]non-3-yl)-5-chloroindazole-3-carboxamide,
N-(endo-9-méthyl-9-azabicyclo[3.3.1]non-3-yl)-1-éthylindazole-3-carboxamide,
5α-N-(2-méthyl-2-azabicyclo[2.2.2]oct-5-yl)-1-méthylindazole-3-carboxamide,
N-(exo-2-méthyl-2-azabicyclo[2.2.1]hept-5-yl)-1-méthylindazole-3-carboxamide,
N-(endo-2-méthyl-2-azabicyclo[2.2.1]hept-5-yl)-1-méthylindazole-3-carboxamide, ou

sel acceptable d'un point de vue pharmaceutique de l'un quelconque des composés ci-dessus.

8. Composé de formule (I) dans laquelle R_2 a la formule (a) ou (c) selon la revendication 1, mais où R_4 ou R_5 est remplacé par un atome d'hydrogène.

9. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 7 ou un sel acceptable d'un point de vue pharmaceutique de ce dernier, et un excipient acceptable d'un point de vue pharmaceutique.

10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 7 dans la préparation d'un médicament destiné à être utilisé en tant qu'antagoniste de la 5-HT.